PDA Global Headquarters
Bethesda Towers,
Suite 600
4350 East West Highway
Bethesda, MD 20814 USA
TEL: +1 (301) 656-5900
FAX: +1 (301) 986-0296

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

29 Dec, 2021

Food and Drug Administration,
Dockets Management Staff (HFA–305),
5630 Fishers
Lane, Rm. 1061, Rockville, MD 20852
Docket No. FDA–2021–D–0432

Re: Microbiological Quality Considerations in Non-Sterile Drug Manufacturing; Draft Guidance for Industry

Dear Madam or Sir,
PDA appreciates the opportunity to comment on FDAs draft guidance on Microbiological Quality Considerations in Non-Sterile Drug Manufacturing; Draft Guidance for Industry; Availability. PDA supports FDA's efforts to enhance guidance in this important area of manufacture for non-sterile products. The PDA commenting committee has developed detailed comments which are provided below.

PDA recommends that FDA review the language surrounding some of the recommendations made and provide clarity as indicated within the comment table attached to this letter.

PDA offers specific feedback for your consideration:

SIGNIFICANT CONCERN – Include references for PDA Technical Report No. 67, (TR 67) Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics. We recommend the inclusion of PDA "TR 67" that included both industry and regulators in the writing of this frequently referenced best practice for the evaluation of objectionable microorganisms. Also consider inclusion of recommendations and reference points from USP Chapter <1111>.

SIGNIFICANT CONCERN- Consider inclusion of examples or case studies where objectionable microorganism assessments or risk frameworks support the presence of low-level bioburden as non-objectionable. This is what the industry needs for guidance as most of the objectionable microorganism assessments pertain to low or enrichment level (no plate counts) microbial recovery. Suggestion: Include some affirming objectionable microorganism risk assessments, such as low-level Gram-negative bacteria in non-aqueous raw materials used in aqueous formulations.
The terms" aqueous" and "non-aqueous" should each be defined.

We suggest the definition of aqueous provided in USP chapter <51> of "water activity of more than 0.6." Non-aqueous should be defined as having a water activity of not more than 0.6.

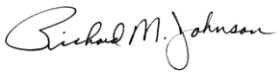
We suggest eliminating the term aqueous-based in favor of the term aqueous. If the term "aqueous-based" is to be used, it should be defined.

PDA would be happy to collaborate with FDA in the continued development of this guidance. Like FDA, PDA is also committed to advancing science to support product quality and patient safety, and the topics covered by this guidance are of special interest throughout our organization.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by a committee of global experts in microbiology on behalf of PDA's Science Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President and CEO

cc: Janie Miller, PDA

U.S. Food and Drug Administration Microbiological Quality Considerations in Non-sterile Drug Manufacturing Guidance for Industry; Docket Number: FDA-2021-D-0432; September 2021

General Comments
Include justification for TR 67. We recommend the inclusion of PDA "TR 67" that included both industry and regulators in the writing of this frequently referenced best practice for the evaluation of objectionable microorganisms.
The guidance has good points about manufacturing process controls and testing with references to compendia and GMPs.
The guidance reads very erratically, with too many instances of footnotes that have additional text that really should be in the main reading flow, instead of asking a reader to go back and forth between text and footnote.
Can any examples or case studies be provided where objectionable microorganism assessments or risk frameworks supported the presence of low level bioburden as non-objectionable? This is what the industry needs for guidance as most of the objectionable microorganism assessments pertain to low or enrichment level (no plate counts) microbial recovery. Suggestion: Include some affirming objectionable microorganism risk assessments. What about low level Gram negative bacteria in non-aqueous raw materials used in aqueous formulations? The terms "aqueous" and "non-aqueous" should each be defined. We suggest the definition of aqueous provided in USP chapter <51> of "water activity of more than 0.6." Non-aqueous should be defined as having a water activity of not more than 0.6. We suggest eliminating the term aqueous-based in favor of the term aqueous. If the term "aqueous-based" is to be used, it should be defined"
Currently there is no glossary is included to define some terms or words needed for understanding the entirety of this document. Addition of a glossary would be beneficial for comprehension of the overall document; for example: Objectionable microorganisms should be defined, according to FDA. Define aqueous and non-aqueous based products (chapters <1112> and <922>).

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28 to 33/1	This guidance discusses product development considerations, risk assessments, and certain CGMPs that are particularly relevant to microbiological control in a manufacturing operation for an NSD. It also provides recommendations to help manufacturers assess the risk of contamination of their NSDs with objectionable microorganisms in order to establish appropriate specifications and manufacturing controls that prevent such	Objectionable microorganism: microorganism that, under certain conditions unique to a product and the associated manufacturing process, poses a risk of causing disease, degrading the quality of a product, or impacting the therapeutic efficacy of a product.

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	contaminations and assure the safety, quality, identity, purity, and efficacy of the NSD.	
129-138/4	Applicable General Chapters,"20 the applicant should ensure that their monograph product complies with the testing requirement, or it could be deemed adulterated. Some of the USP General Chapters that are more commonly referenced in drug monographs, as they apply to controlling microbiological activity in NSDs, include • USP <60> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS TESTS FOR BURKHOLDERIA CEPACIA COMPLEX • USP <61> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: Microbial Enumeration Tests • USP <62> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS:	Add USP General Test Chapter <922> Water Activity to list of compendial chapters.
171-174/5	To ensure product quality and patient safety, it is essential to limit the level and type of microorganisms in NSDs during manufacturing and over product shelf life. While a NSD is not required to be sterile, there is a threshold of microbiological content above which safety and efficacy of a given NSD may be adversely impacted.	The Guidance should provide a threshold or cite USP <1111> for guidance.
180 to 188/6	testing in accordance with established procedures. For instance, water is a common component used in NSD manufacturing. However, water system control deviations can be difficult to detect due to limitations of sampling. These deviations may lead to the formation of biofilms and	Add to paragraph or section 348: (Equipment ancillary to the water system must also be considered for microbial risk. Water must be sampled in a manner consistent with production use, as far as practical (via hose or sample port installed to water delivery piping proximal to the equipment)).

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	have been shown to have a profound impact on microbial quality of an aqueous-based drug. Consequently, proper water system design and control, appropriate microbial action limits, and routine water quality testing is critical to assuring that microbial levels are below established limits, and that the water is free of objectionable microorganisms. Therefore, it is important for manufacturers to have a robust design for water systems, including controls designed to prevent objectionable microorganisms and procedures for monitoring, cleaning, and maintenance.	Therefore, it is important for manufacturers to have a robust design for water systems, including controls designed to prevent objectionable microorganisms and procedures for monitoring, cleaning, sanitization and maintenance. (Periodic passivation of cold water systems should be considered to prevent biofilm formation). The Guidance should be revised to better reflect the intent of USP <1231> in terms of sample size. Eliminate that statement that water should be free of objectionable microorganisms. State that the presence of potentially objectionable microorganisms must be mitigated.
199/6	to preventing objectionable microorganisms from contaminating NSDs	Include 3rd purpose for preservatives, to (control intrinsic bioburden from raw materials/components). But add that (raw materials/components with objectionable or high levels of microorganisms should not be accepted by relying on the preservative to bring into specification.)

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200-203/9	"Certain microorganisms have been found to degrade commonly used preservatives, despite the drug having previously met antimicrobial effectiveness testing acceptance criteria. Consequently, non-sterile drug manufacturers should be aware of the potential for the development of preservative resistance. This potential decrease in preservative effectiveness should be investigated (root cause analysis and corrective action to eliminate the source of contamination) in cases of objectionable microbes or an upward trend in total microbial enumeration counts. "	The current test implies that microorganisms may develop preservative resistance while present in the drug product. The real issue is contamination of poorly preserved aqueous products with preservative resistant organisms such as Bcc that may not have been included in the AET. We suggest rewording this section to state" "Certain microorganisms have been found to degrade commonly used preservatives, despite the drug having previously met antimicrobial effectiveness testing acceptance criteria. Consequently, non-sterile drug manufacturers should be aware of the potential for contamination with preservative resistant organisms (such as Burkholderia cepacia complex which may be capable of growth in weakly preserved products). This potential decrease in preservative effectiveness should be investigated (root cause analysis and corrective action to eliminate the source of contamination) in cases of objectionable microbes or an upward trend in total microbial enumeration counts. "
242/7	...and determining if a specific microorganism is objectionable in the drug product.	...and determining if a specific microorganism is objectionable in the drug product. Reference citation for: (PDA TR-67 Exclusion of Objectionable Microorganisms)
246 to 254/7-8	The controls necessary to prevent objectionable microorganisms will depend on the risk (probability and hazard potential) of microbiological contamination in the NSD, including the characteristics of the NSD (e.g., formulation, component selection, conditions of use, and route of administration), the NSD manufacturing process, and the impact of the manufacturing environment. Well-designed and appropriately controlled manufacturing processes present fewer opportunities for introducing	'Well-designed and appropriately controlled manufacturing processes present fewer opportunities for introducing objectionable microorganisms and their proliferation or growth. (Based on an end-to-end risk assessment of the product and manufacturing process, a well-designed and appropriately controlled manufacturing processes can present fewer opportunities for introducing objectionable microorganisms and their proliferation or growth. In these cases, the reduction in microbiological monitoring (or manufacturing processes and products), use of alternative methods to traditional

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	objectionable microorganisms and their proliferation or growth. For certain low-risk manufacturing operations (e.g., tablet manufacture), reduction in microbiological monitoring and testing may be justified using a risk assessment (see section C below).	microbiological monitoring, and associated testing may be justified using a risk assessment.)
270-274/8	Water Activity □ Water activity of non-aqueous NSDs should be low enough to inhibit microbial growth. □ When NSDs have a higher water activity, there is higher potential for microbial growth and additional manufacturing controls may be needed.	Add a table of the minimum water activity for growth of representative microorganisms. According to the USP chapter <51> definition of aqueous drugs, the water activity of non-aqueous drugs would be 0.6 or less and incapable of supporting microbial growth. We suggest rewording this section to state "Water activity of non-aqueous NSDs should be low enough to inhibit microbial growth."
330 to 332/10	Inadequate equipment cleaning processes, such as extended hold times before cleaning and insufficient drying after equipment has been cleaned, may also promote microbiological contamination.	Inadequate equipment cleaning processes such as extended hold times before cleaning and insufficient drying after equipment has been cleaned, may also promote microbiological contamination (and biofilm formation.)
348-360/10	Water System: Water used as a component (or as a processing aid) must be, as for any other component, of appropriate quality for its intended use in processing and in the formulation. When water used as a component is processed in-house, the purification system must be well-designed and rigorously controlled and maintained. Maintenance and control of water purification systems should include proactive replacement of parts to prevent deterioration and routine monitoring to assure the system can consistently produce water meeting its predetermined quality characteristics. The	Add: (Water systems maintained at >65C helps to control microorganisms and maintain low bioburden levels. There should be proactive sanitization and passivation of the water system to maintain microbial control and the formation of biofilm.)

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	procedure for monitoring should incorporate appropriate action and alert limits and include timely sampling after key water processing steps and equipment used in the water processing and delivery system, including all points-of-use. Water used as a cleaning agent, depending on conditions of use and equipment, should be monitored to ensure it meets appropriate quality for its intended use.	
701/21	"The following seven case studies summarize incidents"	There are nine case studies listed.
823/23	…and corresponding microbial identity testing demonstrated lower preservative amounts in…	The language is unclear and the sentence is hard to follow. It reads as if there was mold growth in the batches, and that there were lower preservative levels in them. The part which is confusing is "and corresponding microbial identity testing". That doesn't seem to belong in this sentence.